UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

In re: OXYCONTIN ANTITRUST LITIGATION	04-MD-1603 (SHS)
PURDUE PHARMA L.P., THE P.F. LABORATORIES, INC. and PURDUE PHARMACEUTICALS L.P., Plaintiffs and Counterclaim Defendants, v. KV PHARMACEUTICAL COMPANY and ACTAVIS TOTOWA LLC, Defendants and Counterclaim Plaintiffs, v. THE PURDUE FREDERICK COMPANY, THE PURDUE PHARMA COMPANY, and EUROCELTIQUE S.A., Counterclaim Defendants.	This document relates to: 07-CIV-3972 (SHS)
PURDUE PHARMA L.P., THE P.F. LABORATORIES, INC., and PURDUE PHARMACEUTICALS L.P., Plaintiffs and Counterclaim Defendants, v. KV PHARMACEUTICAL COMPANY, Defendant and Counterclaim Plaintiff, v. THE PURDUE FREDERICK COMPANY, THE PURDUE PHARMA COMPANY, and EUROCELTIQUE S.A., Counterclaim Defendants.	07-CIV-3973 (SHS) 07-CIV-4810 (SHS)

KV PHARMACEUTICAL'S REPLY BRIEF IN SUPPORT OF ITS CONTENTION THAT PURDUE'S U.S. PATENT NOS. 5,549,912, 5,508,042 AND 5,656,295 ARE UNENFORCEABLE BECAUSE OF PURDUE'S INEQUITABLE CONDUCT

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I. INTRODUCTION

Purdue's attempt to downplay the significance of its repeated reliance on the "surprising discovery" of a reduced, four-fold dosage range benefit for the claimed CR oxycodone formulations cannot succeed. The Purdue patent applicants' and attorneys' repeated assertions that it had been "surprisingly discovered" that the claimed CR oxycodone exhibits a four-fold instead of an eight-fold dosage range effective in controlling pain in 90% of patients were made in such a way as to imply that Purdue had actual scientific evidence of this "discovery", when in fact no such evidence existed. The Federal Circuit found this to be a material omission.

While the Federal Circuit characterized the materiality of Purdue's omission of the fact that the "discovery" was based on insight and not on actual data, despite using language suggesting it did have data, as "not especially high", additional evidence not considered by the Federal Circuit shows that the omission was in fact highly material. Moreover, the evidence makes clear that this omission was made with deceptive intent.

As detailed in KV's opening brief (at 17-19), Purdue's own documents show that Dr. Kaiko and others involved in Purdue's patent applications were well aware that the dosage range benefit was merely theoretical and had not been proven. The egregiousness of Purdue's failure to inform the PTO of this -- which made its allegation of unexpected results an affirmative misrepresentation -- is vastly compounded by the fact that when Purdue actually did conduct clinical studies (PTX 475 and PTX 717) during the prosecution of the patents-in-suit, those studies showed that CR oxycodone and CR morphine were actually comparable in dosage range for 90% of patients.

At the time of the patents' pendency, these were the only studies Purdue had done which provided data regarding the comparative dosage ranges of the two drugs. The results were completely inconsistent with Purdue's representations made to the PTO, which were supported by no data. These clinical studies were robust and well-controlled enough to be formally submitted to the FDA by Purdue. Yet despite the fact that these highly material studies shed significant doubt on -- if not outright disproved -- the alleged "surprising discovery," Purdue did not disclose them to the PTO and never retracted or modified its reliance on the "surprising discovery".

Purdue's excuse for its failure to disclose the studies and its continued and repeated reliance on the four-fold/eight-fold "surprising discovery" is that the studies did not test the particular 10 - 40 mg twice daily dosage range that Purdue discussed in some of its arguments regarding the surprising result of a narrower, four-fold dosage range. This argument fails for several reasons. First, Purdue's primary emphasis when presenting its arguments to the PTO regarding the "surprising discovery" was not on the specific 10 - 40 mg dosage range. Rather, Purdue "sold" the argument to the Examiner on the basis of, as repeatedly stressed by the applicants, the alleged relative reduction of the dosage range as compared to the prior art, MS Contin®.

Second, while Purdue portrays the studies as having "never tested the 10 - 40 mg, twice daily, range" for CR oxycodone (Purdue Br. 37), the range of dosages used in the studies actually overlapped almost completely with the 10 - 40 mg twice daily range, the lower end of the ranges in both studies being 20 mg twice daily (40 mg total daily dose).

Most importantly, Purdue had no data supporting the four-fold versus eight-fold reduced dosage range, 10 - 40 mg or otherwise. The only data Purdue did have for any dosage

range was the contradictory data shown in the studies, which showed that the dosage ranges for the two drugs were comparable. The studies did not show that the CR oxycodone had a narrower dosage range compared to CR morphine. Yet Purdue concealed this data from the PTO, despite the fact that the data, which directly contradicted Purdue's representations about dosage range -- not only ease of titration as focused on by the Federal Circuit -- was reliable enough to submit to the FDA. Regardless of whether the study data would have been sufficient to definitively establish the dosage range reduction for all purposes, such as for an infringement analysis, it was the only available data pertaining to the comparative dosage ranges following titration that Purdue was urging as an unexpected result supporting patentability, and it was in Purdue's possession. It therefore should have been disclosed to the PTO. The failure to do so was a highly material omission which compounded Purdue's omission and concealment of the fact that it had no actual scientific support for the "surprising discovery" despite its repeated statements implying that such support existed.

Purdue's material omission in failing to tell the PTO that the "surprising discovery" was merely based on insight was not made in good faith. Purdue did not merely refer to an insight as a surprising discovery -- it did so knowing that no scientific support existed, and then continued to do so repeatedly while knowing and concealing the fact that it had obtained contradictory scientific evidence that showed that CR oxycodone and CR morphine were actually comparable in dosage range.

Regardless of whether this was the only argument Purdue made for patentability, the Examiner would most certainly have considered this information to be important in considering the allegation of unexpected results. Indeed, the unexpected results allegation was so important to the Examiner that he required Purdue to file the Kaiko Declaration to support it.

(DX 2008, EN205626, Interview Summary Record). The intentional concealment of facts which tended to prove the opposite of Purdue's "surprising discovery" allegation made the repeated assertions of that allegation highly material affirmative misrepresentations which were perpetrated with a clear intent to deceive the PTO into issuing the patents.

The materiality of Purdue's omission, as affirmed by the Federal Circuit, must be viewed in combination with the additional evidence that Purdue not only lacked support for the "surprising discovery", but actually had -- and withheld -- evidence indicating that the alleged unexpected difference between CR oxycodone and CR morphine was not a difference at all. That alleged difference was highly material to the examiner's decision to allow the patents, as shown by Purdue's repeated emphasis of the point and as further illustrated by the Statement of Reasons for Allowance in the '042 prosecution. Purdue's continued reliance on the alleged unexpected difference, despite the fact that the highly material -- but withheld -- study results contradicted it, shows that Purdue's failure to tell the PTO that the allegation was based on an insight, not on data, was deliberate. On balance, that intentional deception, especially when viewed in light of Purdue's possession of the highly material undisclosed study results and its concealment of Dr. Kaiko's relationship with Euroceltique and the parent patent's inventors, weighs strongly in favor of a finding of inequitable conduct and the sanction of unenforceability.

II. ARGUMENT

A. Purdue Relied On A One-Half Reduced Dosage Range In Prosecuting The Patents-In-Suit

Purdue argues that it was not Dr. Kaiko's discovery of the alleged four-fold vs. eight-fold dosage range benefit that was the basis on which the PTO's rejections were overcome, but rather the alleged unpredictability of the in vivo results of CR oxycodone in comparison to the prior art CR opioids. However, while it is true that the patent claims were written in terms of

the in vivo parameters of C_{max} and T_{max}, those parameters per se (which were certainly not unpredictable the fifth time Purdue used a new CR opioid)[1] did not serve to distinguish the claimed invention over the prior art unless they achieved some unexpected result. Purdue argued over and over again to the PTO that this unexpected result was the reduced (four-fold) dosage range.

Purdue also argues that the unexpected result or "surprising discovery" relied on during prosecution was not that CR oxycodone unexpectedly controls pain over a four-fold range as opposed to an eight-fold range in about 90% of patients, but rather that it was a "particular" four-fold range of CR oxycodone, i.e. 10 - 40 mg twice daily, that had this property, and that therefore the Kalso and Berman studies (which tested total daily dosages of 40 mg and up)[2] are irrelevant. Purdue also argues that the Kaiko Declaration actually did not rely on the reduced dosage range, pointing out that the declaration refers to a published survey article (Inz Remand Ex. 1)[3] which was not attached to the declaration. Purdue argues that the declaration does not

[1] Purdue argues that its characterization of achieving 12 hours of pain relief with a T_{max} of 2 - 4 hours for CR oxycodone as "surprising" was justified because the term "surprising" is "common" in patent prosecution, and because it was not possible to predict analgesic effect in related opioids without testing. (Purdue Br. 27-32). This does not explain, however, how the "discovery" that use of oxycodone in a matrix having the same in vitro dissolution profile as MS Contin® resulted in the same in vivo results, providing a 2 - 4 hour T_{max} and 12 hours of pain relief, was "surprising", given that oxycodone was the fifth opioid -- following morphine, dihydrocodeine, codeine, and hydromorphone -- for which Purdue had obtained the same results in the same way. Purdue's argument that "surprising" is a "common term in patent prosecution" is of no moment. In fact, it was on the very basis of alleged "surprising" results that Purdue obtained the patents, i.e. by arguing that unexpected and "surprising" results were evidence of nonobviousness.

[2] As discussed infra, to compare apples to apples, a 40 mg total daily dose is actually a dose of 20 mg, taken twice daily.

[3] KV does not oppose Purdue's motion to supplement the record (MDL D.I. 183). None of the new exhibits or testimony Purdue seeks to add to the record, however, ultimately have any

directly refer to the attachment that actually was attached to it, which set forth that the CR oxycodone formulation "can be used over approximately ½ the dosage range as MS Contin® to control 90% of patients with significant pain." (DX 2008, EN205640, '331 file history, Paper 8, Mar. 9, 1993, attachment p. 3). Both of these arguments are without merit.

As detailed in KV's opening brief, Purdue repeatedly argued during prosecution that the invention was non-obvious because of the surprising discovery that the invention was effective over a dosage range that was twice as narrow as MS Contin®. While it is true that a 10 - 40 mg dosage range was mentioned, the major thrust of Purdue's arguments was that the CR oxycodone could be used over a dosage range that was twice as narrow as that of MS Contin®, which was important because a narrow range would be a contributing factor towards ease of titration.

For example, Purdue did not say that it had been surprisingly discovered that the formulations were effective over a 10 - 40 mg range versus some specific eight-fold range for other opioid analgesics, e.g., 10 - 80 mg, 5 - 40 mg, or 20 - 160mg. Rather, the applicants stressed the "sharp contrast" between four-fold and eight-fold, and the fact that the invention "can be used over approximately ½ the dosage range" as compared to CR morphine. (E.g., DX 2008, EN205619-20; '331 file history, Paper 4, Oct. 22, 1992, pp. 3-4).

Thus, during the prosecution of the '912 patent, in response to the PTO's rejection, the applicants argued again that the CR oxycodone "can be used over approximately ½ the dosage range as compared to commercially available controlled-release morphine formulations." (DX 2033, P000177, '912 file history, Paper 8, Feb. 22, 1995, p. 3). Purdue's

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bearing on the issue of whether Purdue committed inequitable conduct in procuring the patents-in-suit.

argument presented to the Examiner did not state that the surprising discovery was that a particular four-fold dosage range was effective rather than a particular eight-fold range, but rather argued much more broadly that the CR oxycodone formulation can be used over about ½ the dosage range of CR morphine without mentioning a specific 10 - 40 mg range. Purdue's remarks read:

> The presently claimed invention . . . is directed to formulations . . . containing from about 10 to about 160 mg of oxycodone or a salt thereof which are chosen so that a mean maximum peak plasma concentration of oxycodone of from about 6 to about 240 ng/ml is obtained *in-vivo* from a mean of about 2 to about 4.5 hours after administration and a mean minimum plasma concentration of from about 3 to about 30 ng/ml is obtained *in-vivo* from a mean of about 10 to about 14 hours after steady state conditions are achieved by repeated 12 hour administrations.
>
> The present invention is directed in part to the surprising discovery that by choosing the above-identified parameters in the controlled-release formulation, it is possible to acceptably control pain over a substantially narrower dosage range than through the use of other opioid analgesics of similar chemical structure. Thus, Applicants have surprising found that even in the case of controlled-release opioid formulations having a similar *in-vitro* release profile, a much wider range of dosage of drug must be administered to the patient in order to achieve a satisfactory analgesic response over the requisite period of time. This is set forth, e.g., in the Specification at page 6, line 30, through page 7, line 3.[4] Therein it is mentioned that the despite the fact that both control-release oxycodone and control-release morphine administered every 12

[4] The cited passage from the '912 specification reads:

> Despite the fact that both controlled-release oxycodone and controlled release morphine administered every 12 hours around-the-clock possess qualitatively comparable clinical pharma-cokinetic characteristics, the oxycodone formulations of the presently claimed invention can be used over approximately ½ the dosage range as compared to commercially available controlled release morphine formulations (such as MS Contin®) to control 90% of patients with significant pain.

(DX 2033, P000067-68, '912 application, pp. 6-7).

> hours possess qualitatively comparable clinical pharmacokinetic characteristics, the oxycodone formulations presently claimed can be used over approximately ½ the dosage range as compared to commercially available controlled-release morphine formulations.
>
> The above result is surprising and of extreme clinical importance in that the clinician is able to identify the dose of oxycodone which will control pain in a wide variety of patient populations while reducing the duration of unacceptable pain that individual patients must endure during the opioid analgesic titration process. Furthermore, to the pharmaceutical manufacturer, the presently-claimed invention represents a step forward in the preparation of control-release dosage forms because now it is possible to adequately dose a wide range of patient populations with relatively few solid dosage forms. Previously, in view of the wide variability of doses needed to provide effective analgesia in such patients, a greater number of dosage forms having different amounts of opioid would have to be available to the clinician in order to correctly titrate these patients.

(DX 2033, P000176-78, '912 file history, Paper 8, Feb. 22, 1995, pp. 2-4 (emphasis added)). There is no mention of a specific 10 - 40 mg dosage range in this passage. Purdue represented in this submission to the Examiner that the invention provided the unexpected result of a narrower dosage range, without limiting that representation to any particular four-fold range.

Similarly, when Dr. Kaiko testified on direct examination at the Endo trial regarding the four-fold versus eight-fold benefit of the invention, he did not speak of any specific four-fold dosage range, 10 - 40 mg or otherwise. (Tr. 173-177 (testimony regarding demonstrative exhibit PTX 1061, a graphical representation entitled "CR Oxycodone: Narrower Range of Dosages Than CR Morphine," which also does not specify any particular numerical dosage range)).

As for Purdue's argument that the Kaiko Declaration submitted during the parent '331 prosecution did not rely on the reduced dosage range as an unexpected result, the facts speak for themselves. Prior to the submission of the declaration, Purdue had submitted, in

attorney arguments, the alleged "surprising result" of the four-fold dosage range as a response to the PTO's obviousness rejection. (DX 2008, EN205618-21, '331 file history, Paper 4, Oct. 22, 1992, pp. 2-5). The Examiner's reaction to these arguments was to require the applicants to submit a "declaration supporting unobviousness and unexpected results." (Id., EN205626, Interview Summary Record). The Examiner clearly felt that the alleged unexpected results would be sufficient to support patentability, but only if set forth via a sworn declaration. In response, the Kaiko Declaration was submitted, which included the attachment which set forth the four-fold versus eight-fold advantage.

Purdue now attempts to distance itself from the Kaiko attachment, claiming that a different exhibit should have been attached to the declaration. But that other exhibit was not attached; the Kaiko attachment was, and it was immediately after the Kaiko attachment was submitted that the '331 claims were allowed. Moreover, while Purdue claims that the Kaiko attachment was included in its submission in error, this claim rings hollow. Purdue never made any attempt to correct this "error", and the Kaiko attachment provided exactly what the Examiner had requested: support for the unexpected results allegation in the form of a sworn declaration. Later, the same "surprising discovery" of the four-fold dosage range was added to the specifications of the applications for the '912, '042, and '295 patents, and Dr. Kaiko was included as an inventor. Purdue continued to rely on the "discovery" in its argument for patentability, as discussed above, and the Examiner cited it in the statement of reasons for allowance of the '042 patent. (DX 2009, EN205735).

B. Purdue Misrepresented Dr. Kaiko As An Independent Expert

As noted in KV's Opening Brief at 15-16, when Purdue submitted the Kaiko Declaration, it failed to inform the Examiner that Dr. Kaiko was in fact a co-worker of the '331

inventors or that Kaiko's employer, Purdue, was closely affiliated with the assignee of the application, Euroceltique, creating the false impression that Kaiko was independent and unbiased.

Purdue argues that this failure should be excused because the Examiner "made no request for a 'disinterested' declarant." (Purdue Br. 33). However, by asking for a sworn declaration supporting the asserted unexpected results, the Examiner clearly wanted that declaration to come from an unbiased declarant, or at the very least would have found it important to know whether there was any connection between the declarant and the applicants or their attorneys or employer. Otherwise there would have been no point in requesting the declaration.

As the Federal Circuit has very recently confirmed, failure to inform the examiner of the relationship between a declarant and the inventor, even where the "examiner . . . did not request an affidavit from a disinterested party" and even where there was no substantive error in the affidavit, can be a basis for a holding of unenforceability due to inequitable conduct. Nilssen v. Osram Sylvania, Inc., No. 2006-1550, 2007 U.S. App. LEXIS 23733, at *4, 11 (Fed. Cir. Oct. 10, 2007) (emphasis added). The court stated:

> We conclude that the district court did not abuse its discretion in holding that Nilssen engaged in inequitable conduct with respect to the '345 and '690 patents by submitting affidavits by Fiene in support of patentability, including points of distinction over prior art patents, without informing the examiner of the affiant's relationship to Nilssen. Even though the examiner did not raise a question concerning any such relationship, it is material to an examiner's evaluation of the credibility and content of affidavits to know of any significant relationship between an affiant and an applicant, see Ferring B.V. v. Barr Labs., Inc., 437 F.3d 1181, 1187-88 (Fed. Cir. 2006); failure to disclose that relationship violated Nilssen's duty of disclosure.

Id. at *11-12.

Purdue further claims that the PTO was already aware of Dr. Kaiko's relationship with the inventors and Euroceltique because the PCT application that led to the '912 patent listed Kaiko as an inventor. Purdue notes that the PCT International Search Report that was mailed to Purdue's attorneys on March 17, 1993 (Inz Remand Exh. 6) revealed that the same Examiner (James Spear) who was handling the '331 application also handled that PCT search,[5] and speculates that the Examiner therefore "received information about the relationship" before the Kaiko Declaration was considered. (Purdue Br. 34-35). But this cannot be evidence of good faith on Purdue's part, because as of the time the Kaiko declaration was submitted, March 9, 1993 (a week before the PCT search was mailed), as far as Purdue knew, the Examiner had no way of learning of the connection even if he wanted to.[6]

A patent applicant is bound by the duty of candor, 37 C.F.R. §1.56, to be forthcoming with the PTO, and not to assume that the PTO will pick up on cryptic clues or do its own investigation of the relationship between a declarant and the applicant. Even if Purdue had known as of the time the Kaiko Declaration was submitted that the PCT application and the '331 application were being handled by the same examiner (it did not), it has been held that a PTO

[5] Although Examiner Spear is listed as "Authorized Officer" on the March 17, 1993 PCT search report, he did not sign it; it is signed by a person named Briggs, "for" Mr. Spear. (Inz Remand Exh. 6 at P206099, P206103).

[6] Purdue also points out that the Kaiko Attachment includes Dr. Kaiko's CV, and that that CV identifies eight publications or abstracts on which Dr. Kaiko was listed as a co-author with Oshlack, one of the '331 inventors. (Purdue Br. 34, citing DX 2008, EN205642-58). Purdue does not mention, however that these eight publications are buried among a 14-page list of some 192 items. For Purdue to point this out now is illustrative of its attitude toward the duty of candor. The Examiner can hardly have been expected to sift through the list of publications and notice or make the connection that Oshlack and Kaiko were co-authors of a few of them. Even if he had, there is no indication that they worked for the same employer. The CV identifies Dr. Kaiko's employer as The Purdue Frederick Company, and contains no mention of Euroceltique, the '331 assignee.

examiner cannot be assumed to be aware of every detail of every application that comes across his desk, and such assumed knowledge is no excuse for nondisclosure.

As the Federal Circuit has stated, "a prosecuting attorney should not 'assume that a [PTO examiner] retains details of every pending file in his mind when he is reviewing a particular application.'" McKesson Info. Solutions, Inc. v. Bridge Med., Inc., 487 F.3d 897, 925 (Fed. Cir. 2007) (quoting MPEP §2001.06(b) (5th ed. Rev. 3, 1986) and Armour & Co. v. Swift & Co., 466 F.2d 767, 779 (7th Cir. 1972)) (case involving related applications). "The duty of candor and good faith exists to ensure that patent applicants provide accurate material information to the PTO so that the examiner can efficiently and effectively assess their claims." Ariad Pharms., Inc. v. Eli Lilly & Co., No. 02-11280-RWZ, 2007 U.S. Dist. LEXIS 49076, at *45-46 (D. Mass. July 6, 2007) (holding that "duty of candor is not so lax that it requires an examiner" to sua sponte track corresponding aspects of related applications).

The Examiner, by asking for a declaration regarding the alleged unexpected results, clearly contemplated that the declarant would be unbiased. At the very least, any potential bias would have been highly material. The very fact that a CV was attached to the Kaiko Declaration, and the fact that the Declaration expresses Dr. Kaiko's "opinions", confirms that it was being presented as the declaration of an unbiased expert, not a co-worker of the inventors. Purdue's deceptive submission of the Kaiko Declaration as if it was coming from an unbiased expert, concealing the fact that it actually was coming from a co-worker, is additional evidence of inequitable conduct that renders the '331 patent and its progeny unenforceable.[7]

[7] KV did not "fail" to take the deposition of Mr. Steinberg as Purdue suggests. (Purdue Br. 35). KV submitted its briefing on the inequitable conduct issue based on the record of the Endo case as the Court directed.

C. The Clinical Studies Submitted To The FDA Were Contradictory To Purdue's Patentability Arguments But Were Concealed From The PTO

The Kalso and Berman studies were contradictory to Purdue's allegations of unexpected results, and the nondisclosure of this highly material information constitutes strong evidence that Purdue's reliance on its misleading characterization of what was only an insight as a "surprising discovery" supported by scientific evidence cannot have been in good faith, but rather was made with intent to deceive the PTO.

As discussed in KV's opening brief, the Kalso and Berman (Mucci-LoRusso) clinical studies contradicted Purdue's representations to the PTO that the invention controlled pain using only a four-fold dosage range "in sharp contrast" to the eight-fold dosage range required for the CR morphine prior art. (KV Br. at 25-34). These studies found that there was no significant difference in the time to achieve stable pain control (i.e. time to titrate) between CR oxycodone and CR morphine, as confirmed by the testimony of Dr. Goldenheim (Id. at 26-27, 29, 30). Significantly, the studies also found that the final dosage ranges for the two drugs were not four-fold and eight-fold, but rather were equivalent or comparable in terms of their narrowness. (Id. at 28-30).[8]

[8] Dr. Kaiko attempted at trial to escape the conclusions of the Berman study by disingenuously claiming that the study was not designed to draw conclusions about titratability, even though the study expressly drew such conclusions and labeled them as "Conclusions". (KV Br. at 32-33; Tr. 421-23; PTX 717 at P187423). Similarly, Purdue claims that the studies' observations about the lack of difference in titration between OxyContin® and MS Contin® may not have been statistically significant and were not conducted the way titration is done in the real world. (Purdue Br. 37). However, the studies specifically conclude that the time to achieve stable pain control was the same for both drugs (KV Br. at 26, 29). More importantly, separate from the ease of titration issue, the dosage range results of both studies were contrary to Purdue's representations to the PTO about the allegedly narrower dosage range of CR oxycodone as compared to prior CR opioids such as MS Contin®.

Purdue responds that the Kalso and Berman studies did not test the specific dosage range 10 - 40 mg. As discussed above, however, Purdue's arguments to the PTO were not limited to a 10 - 40 mg range; Purdue repeatedly stressed the alleged four-fold versus eight-fold and the "½ the dosage range" distinctions without limitation. Further, the studies were the only actual data Purdue had during the prosecution of the patents-in-suit as to the relative dosage ranges, since Dr. Kaiko's "insight" is not data.

Moreover, Purdue's premise that the studies did not test the 10 - 40 mg range is overstated. The 10 - 40 mg range is expressed as a twice daily dosage, 10 - 40 mg twice daily (or "q12h", meaning every 12 hours), while the dosage data listed in the studies (as reproduced in KV's Opening Brief at 28, 30) are expressed as total daily dosages (i.e. 24 hours). Thus, the 10 - 40 mg twice daily range is actually equivalent to a total daily dose of 20 - 80 mg, overlapping with the total daily dosage ranges of CR oxycodone tested and reported in the Berman and Kalso studies of 40 mg and up (see PTX 475, P275657; PTX 717, P187387 (both confirming that the lowest dose of CR oxycodone given in the studies was 20 mg q12h)).

Stated another way, in terms of q12h dosages, both the Kalso and Berman studies tested dosages of 20 mg twice daily and up, overlapping with the 10 - 40 mg q12h range. Thus, the only part of the 10 - 40 mg range for CR oxycodone actually not tested in the Kalso and Berman studies was the 10 mg dosage amount, and the ranges found to be effective in the Kalso and Berman studies almost completely overlapped with the 10 - 40 mg range. The study results thus would have been contradictory to Purdue's "surprising discovery" of the narrower dosage range benefit even if that alleged discovery had been limited to the 10 - 40 mg range, which, as noted above, it was not.

Purdue contends that this Court previously considered the "identical argument" concerning the studies and rejected it. This is not correct. The Court did note the difference in dosage ranges between the studies and the 10 - 40 mg range in its prior decision. Purdue Pharma, LP v. Endo Pharmaceuticals Inc., 70 U.S.P.Q.2d 1185, 2004 U.S. Dist. LEXIS 10 at *47-48 (S.D.N.Y. Jan. 5, 2004), aff'd in part, vacated in part, 438 F.3d 1123 (Fed. Cir. 2006). The Court found that it was not clear what conclusions could be drawn from the studies given the fact that the studies did not test the 10 mg dosage amount.

The Court's comments, however, were not made in the context of inequitable conduct. Rather, they were made in the context of the Court's infringement analysis, i.e., the issue of whether the OxyContin® composition actually exhibits a four-fold dosage range and thus whether that composition would be covered by the claims (an issue later mooted by the Federal Circuit's disposition of the claim construction issue, 438 F.3d at 1137). The Court found the 1996-2001 NDTI data regarding dosages to be more helpful. Regardless of the probative value of the NDTI data, however, that data was not in Purdue's possession during prosecution. The studies were. The issue here is not whether the studies proved the exact dosage range to a certainty, but whether Purdue satisfied its duty of candor to the PTO by representing the four-fold dosage range as an unexpected beneficial result supporting non-obviousness, even though that alleged range had not been proven and even though the Kalso and Berman studies, which were not idle notes or quick and dirty tests, but rather clinical studies submitted to the FDA, on their faces directly contradicted Purdue's representations and at the very least tended to refute Purdue's arguments for patentability.

Purdue also argues that the fact that the Kalso and Berman studies were conducted for purposes of FDA approval of comparative claims regarding ease of titration, for

which the FDA's standards of proof are high, makes the studies irrelevant to Purdue's assertions to the PTO. This is incorrect. Regardless of the intended purpose of the studies, their findings, and in particular the dosage range data those findings were based on, were inconsistent with Purdue's reliance in the PTO on the four-fold versus eight-fold dosage range comparison in support of patentability. Nor does the fact that ease of titratability is a benefit or advantage of the invention, rather than a claim term, affect the studies' relevance.

While Purdue is correct that the range of dosages and ease of titration are different concepts, they are clearly related, and Purdue relied on both in arguing that the invention provided unexpected results. As the Court noted in its prior decision, one of the factors affecting ease of titration is the breadth of the required dosage range for treating the population of patients, and the statements in Purdue's internal documents to the effect that the titratability advantage of CR oxycodone had not been proven at the time Purdue made its "surprising discovery" claims are directly relevant to Purdue's assertions regarding relative dosage range:

> a reduced dosage range is directly related to easier titration; any concerns about proving the latter must affect belief in the former, especially as Purdue's reduced dosage range assertion is – like the titration assertion – made in a comparative context – i.e., "other opioid analgesics require approximately twice the dosage range."
>
> Accordingly, . . . any good faith belief that Purdue had "discovered" the reduction in dosage range is substantially undercut by its admitted inability to prove, or even to develop, a "set of procedures and methods" to prove this reduction in dosage range (and related ease of titration) and cannot "overcome an inference of intent to mislead."

Purdue, 2004 U.S. Dist. LEXIS 10, at *83-84 (citations omitted).

The Court need not and should not, however, rely solely on Purdue's statements regarding its inability to prove ease of titration marketing claims at the time the "surprising discovery" representations were made to the PTO. Aside from concluding that ease of titration

was comparable for the two drugs being compared, the Kalso and Berman studies also contained data as to the final dosages arrived at after titration was completed for the population of patients tested. This underlying data failed to show a ½ reduction in dosage range for CR oxycodone versus CR morphine (four-fold vs. eight-fold or otherwise). This data, separate and apart from any conclusions that titratability was comparable, was contradictory to the representations made by Purdue to the PTO.

The relevance of this underlying data is not affected by the higher standard of proof used by the FDA in evaluating marketing claims. Data is data. Indeed, the fact that the data is contained in full-fledged studies that were actually submitted to the FDA bolsters its value, as well as the conclusion that Purdue itself viewed these studies -- and the data in them -- as valid and meaningful. The data contained in the studies was the only data Purdue had regarding the relative dosage ranges; it was the best test Purdue had for measuring this parameter, and the studies were deemed good enough to submit to the FDA. Yet Purdue withheld this contradictory data from the PTO -- a highly material omission by any standard -- and continued to rely on the ½ dosage range reduction.

Purdue purports to distinguish Merck & Co., Inc. v. Danbury Pharmacal, Inc., 873 F.2d 1418, 1422 (Fed. Cir. 1989), which held that the simultaneous submission of data to the FDA and withholding of that same data from the PTO was "damning" evidence of intent to mislead the PTO, on the ground that in Merck, the statements made to the PTO were inconsistent with the statements made to the FDA. (Purdue Br. 19).

As noted in KV's Opening Brief (p. 35), however, Purdue's argument ignores Merck's submission of amitriptyline data to the FDA while withholding that data from the PTO, which was a separate act considered by the court in arriving at its finding of inequitable conduct,

and moreover, that Purdue did in fact make inconsistent disclosures to the FDA and the PTO just as occurred in Merck. Purdue submitted studies to the FDA containing dosage range data indicating that CR oxycodone and CR morphine had comparable dosage ranges, while it continued to represent to the PTO that those dosage ranges were not comparable, but rather four-fold and eight-fold, and to imply that it had scientific evidence of this when in fact it had no such evidence at all.

Similarly, Purdue purports to distinguish Cargill, Inc. v. Canbra Foods, Ltd., 476 F.3d 1359 (Fed. Cir. 2007), discussed in detail in KV's Opening Brief at pp. 35-37, on the ground that in Cargill the undisclosed test data was inconsistent with and contradicted the data disclosed in the patents at issue. Purdue's argument is based entirely on its position that the Kalso and Berman studies were not inconsistent with the representations made to the PTO because the studies "did not conclude . . . anything about the properties of the 10 - 40 mg dosage range, because that range was not tested." (Purdue Br. 39). As discussed supra, Purdue's premise is wrong. The tested ranges overlapped almost completely, and more importantly, Purdue's arguments for patentability relied on the relative four-fold vs. eight-fold, ½ dosage range reduction, and was not limited to a "particular" dosage range.

Therefore, when Purdue obtained the Kalso and Berman data showing that its claim of superiority of the dosage range of CR oxycodone would be called into question by that data, which was the only data available to Purdue regarding the relative dosage ranges and comparative titratability of CR oxycodone and CR morphine, it had a duty to disclose that data to the PTO. As the Cargill court stated,

> "[M]ateriality is determined from the viewpoint of a reasonable patent examiner, and not the subjective beliefs of the patentee". . . .

> A reasonable examiner would certainly want to consider test data that is directly related to an important issue of patentability. . . .

Id. at 1366 (citation omitted); 1367 ("'[c]lose cases should be resolved by disclosure, not unilaterally by the applicant'"; applicants should not make or rely "'on their own determinations of materiality'" (citations omitted)).

Purdue cites Impax Labs., Inc. v. Aventis Pharms., Inc., 468 F.3d 1366, 1377-78 (Fed. Cir. 2006) in arguing that it had no duty to present the studies to the Examiner and then try to explain them away instead of withholding them. Impax is inapposite because it involved data that was held not to be material. Here, the Federal Circuit has already affirmed that Purdue's "surprising discovery" misrepresentation was material, and as set forth above, the studies were highly material.

The failure to disclose the study data creates a strong inference that Purdue's representations alleging that it had "surprisingly discovered" the unexpected result of a reduced dosage range, despite the fact that it had no actual data to support that claim, had been made with an intent to deceive the PTO. Even after Purdue became aware of the study data, it persisted in relying on the "surprising discovery" and withheld the contrary data from the PTO, because otherwise Purdue would have been forced to reveal that its "discovery" of unexpected dosage range results was not in fact supported by any scientific data, but was only supported by Dr. Kaiko's insight all along. This is strong evidence of intent to deceive.

III. CONCLUSION

For the reasons set forth above and in KV's Opening Brief, KV respectfully urges this Court to declare the '912, '042 and '295 patents unenforceable.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that I caused a true and correct copy of **KV PHARMACEUTICAL'S REPLY BRIEF IN SUPPORT OF ITS CONTENTION THAT PURDUE'S U.S. PATENT NOS. 5,549,912, 5,508,042 AND 5,656,295 ARE UNENFORCEABLE BECAUSE OF PURDUE'S INEQUITABLE CONDUCT** to be served on October 19, 2007 via CM/ECF to all the listed parties.

s/ John F. Sweeney
John F. Sweeney